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Protected Amino Acid Chlorides vs Protected Amino Acid Fluorides: Reactivity Comparisons.

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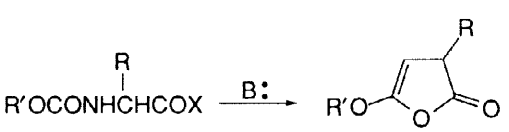
Abstract: Although Fmoc amino acid fluorides are excellent reagents for coupling of moderately hindered amino acids (*e.g.*, Aib-to-Aib) they are not suited for significantly more hindered systems (*e.g.*, Aib-to-MeAib). While urethane-protected acid chlorides are inherently more reactive than the fluorides they are also ineffective for hindered systems due to competing oxazolone formation. This limitation is by-passed if urethane protection is replaced by arenesulfonyl protection and the Aib-to-MeAib and even the MeAib-to-MeAib couplings are easily achieved via the appropriate acid chlorides but not the acid fluorides.

Previous studies on the reactivities of simple carboxylic acid halides have revealed differing relative orders depending on the nature of the test nucleophile.[1] With neutral oxygen nucleophiles such as H_2O or MeOH the fluorides are significantly less reactive than the chlorides but the reverse has been observed for hydroxide ion.[2] With amines the "normal" order I > Br > Cl > F was followed for the benzoyl halides.[3] These results are expected where C–X bond breaking is important at the transition state for substitution. Presumably in the case of hydroxide or alkoxide ion the increased stabilization of the tetrahedral intermediate due to the enhanced C–F dipole effect is responsible for the increased reactivity of the acid fluoride, an effect which is also commonly seen in the mechanistically related substitution reactions of aryl halides bearing *o*- and/or *p*-electron-withdrawing substitutents.[4]

Compared with simple acid halides such as the acetyl or benzoyl derivatives, N-alkoxycarbonyl (urethane) protected amino acid halides **1** occupy a special position due to their base-catalysed conversion to oxazolones **2**.[5] The recently discovered urethane-protected amino acid fluorides **1**, X = F, were remarkably



1, X = Cl, Br **2** eq. 1

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resistant to this conversion, a fact which was taken to rationalize the more satisfactory application of the fluorides to solid phase peptide synthesis in comparison with the corresponding chlorides[5b,6] or bromides.[7] In addition to their use with the proteinogenic amino acids, the protected amino acid fluorides could be routinely extended to the difficult coupling of α-aminoisobutyric acid (Aib) residues.[8] Even more hindered systems such as 9-fluorenemethyloxycarbonyl-N-methyl-Aib-F (Fmoc-MeAib-F) could be coupled to H-Aib-OMe, most effectively in the presence of a silylating agent such as bis(trimethylsilyl)acetamide (BSA).[9,10]

Coupling to the amino group of N-methylaminoisobutyric acid is at least an order of magnitude more difficult than coupling to its carboxyl function[11] and such couplings, *e.g.*, Fmoc-Aib-F to H-MeAib-OMe, were next examined. The only previous example located, that of N-(benzyloxycarbonyl)-Aib-OH to H-MeAib-NHMe, required treatment with bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP) in the presence of diisopropylethyl amine (DIEA) for two weeks at room temperature to give the protected dipeptide amide in 3% yield.[12] Even unhindered amino acids (Phe, Ala) are difficult to couple to MeAib residues.[13]

In the present work extensive comparisons of the reactions between Fmoc-Ala-X or Fmoc-Aib-X (X = Cl, F) and H-Aib-OMe or H-MeAib-OMe have been carried out. The Aib-Aib couplings via the acid chloride were marred by the expected oxazolone effect (Fig. 1). For Fmoc-Ala-Cl in the presence of BSA nearly complete coupling to H-MeAib-OMe occurred within 30 min whereas the corresponding acid fluoride reacts under the same conditions only to the extent of 3% and even after 24 h the reaction was only 24% complete (Fig. 2). Thus for the less hindered normal amino acid chlorides peptide bond formation readily competes with oxazolone formation, and for highly hindered substrates the chlorides are clearly more reactive than the fluorides.

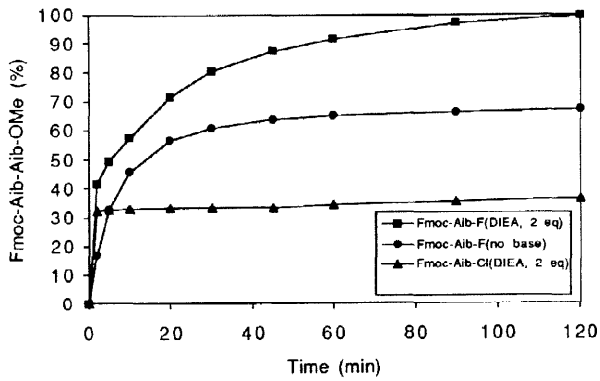


Fig. 1. Time course for the reaction of Fmoc-Aib-X (Cl, F) with H-Aib-OMe in dichloromethane

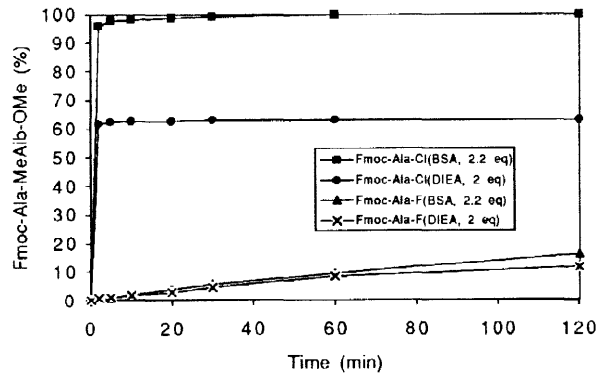
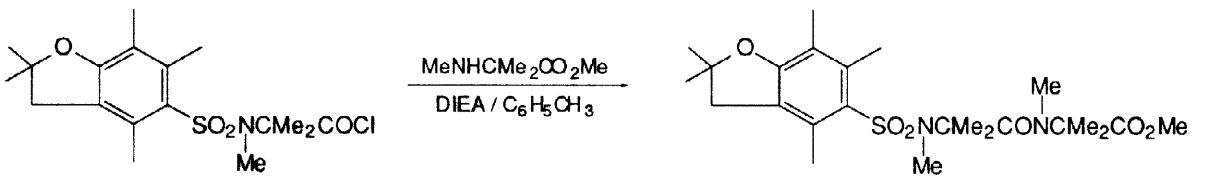


Fig. 2. Time course for the reaction of Fmoc-Ala-X (Cl, F) with H-MeAib-OMe•HCl in dichloromethane

Upon increasing the steric requirements of the electrophile beyond that of alanine, the reaction was greatly inhibited and no coupling could be achieved between Fmoc-Aib-F or even Fmoc-Aib-Cl and H-MeAib-OMe in the presence of either DIEA or BSA. With hindrance of this magnitude the practical limit for urethane-based amino acid coupling appears to have been reached. This led to a consideration of other N-protecting groups for which oxazolone formation, even for the acid chloride, is precluded. Indeed early

studies[11] showed that N-(*p*-toluenesulfonyl)-Aib-Cl (Ts-Aib-Cl) was effective in the coupling of Aib-to-Aib systems provided that non-aqueous media were used to avoid degradation[14] of the acid chloride. In the absence of other influences, the greater inductive effect of a sulfonyl residue relative to that of a carbonyl group[15] was expected to increase the reactivity of a sulfonyl substituted amino acid halide over that of its carbamoyl counterpart. In line with this expectation, Ts-Aib-Cl reacted readily with H-MeAib-OMe. If this reactivity enhancement also obtains in the case of the acid fluoride it is insufficient since Ts-Aib-F could not be made to acylate H-MeAib-OMe.

To make practical use of this observation the tosyl group was substituted by the related but more easily deblocked 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf)[16] residue. By maintaining anhydrous conditions with toluene as solvent this coupling could be achieved (63%) even in the case of the extremely hindered MeAib-to-MeAib coupling (eq. 2).



3 4 eq. 2

Deblocking of the Pbf residue could be carried out via trifluoroacetic acid (TFA)/Me_2S, thus making further chain extension possible.[17]

REFERENCES AND NOTES

1. For a brief review on the reactivity of protected amino acid halides and references to previous studies on the reactivity of simple acid halides, see (a) Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acct. Chem. Research.* **1996**, *29(6)*, 268 and (b) Footnote 11 of ref. 6.
2. Recently a similar effect was reported in which the alkoxide anion derived from a highly hindered alcohol reacted with a cyclohexenecarboxylic acid fluoride to give the ester in significantly higher yield (70%) than the corresponding acid chloride (35%). See Mayer, S.; Joullie, M. M. *Syn. Commun.* **1994**, *24*, 2367.
3. Bender, M. L.; Jones, J. M. *J. Org. Chem.* **1962**, *27*, 3771.
4. Bunnett, J. F.; Garbisch, E. W. Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385.
5. (a) Benoiton, N. L. *Biopolymers* **1996**, *40*, 245; (b) Carpino, L. A.; Chao, H.-G.; Beyermann, M.; Bienert, M. *J. Org. Chem.* **1991**, *56*, 2635.
6. Carpino, L. A.; Sadat-Aalaee, D.; Chao, H.-G.; DeSelms, R. H. *J. Amer. Chem. Soc.* **1990**, *112*, 9651.
7. Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401, footnote 20.
8. (a) Wenschuh, H.; Beyermann, M.; Krause, E.; Brudel, M.; Winter, R.; Schümann, M.; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1994**, *59*, 3275. (b) Wenschuh, H.; Beyermann, M.; Haber, H.; Seydel, J. K.; Krause, E.; Bienert, M.; Carpino, L. A.; El-Faham, A. *J. Org. Chem.* **1995**, *60*, 405.

9. Wenschuh, H.; Beyermann, M.; Winter, R.; Bienert, M.; Ionescu, D.; Carpino, L. A. *Tetrahedron Lett.* **1996**, *37*, 5483.
10. BSA may act both as base and N-silylating agent. The effect of prior silylation on coupling processes carried out using amino acid halides will be described in the full description of this work.
11. Leplawy, M. T.; Jones, D. S.; Kenner, g. W.; Sheppard, R. C. *Tetrahedron* **1990**, *11*, 39.
12. Moretto, V.; Valle, G.; Crisma, M.; Bonora, G. M.; Toniolo, C. *Int. J. Biol. Macromol.* **1992**, *14*, 178.
13. Spencer, J. R.; Antonenko, V. W.; Delaet, N. G. J.; Goodman, M. *Int. J. Pept. Prot. Res.* **1992**, *40*, 282.
14. (a) Wiley, R. H.; Miller, J. G.; Day, A. R. *J. Am. Chem. Soc.* **1954**, *72*, 3496; (b) Beecham, A. F. *J. Am. Chem. Soc.* **1957**, *79*, 3527.
15. (a) Price, C. C.; Oae, S. *Sulfur Bonding*, Ronald Press, New York, NY, 1962, p. 120; (b) A similar effect may be operative in the greater Friedel-Crafts reactivity of N-phthaloylamino acid chlorides relative to N-methoxycarbonylamino acid chlorides. See Effenberger, F.; Steegmüller, D. *Chem. Ber.* **1988**, *121*, 117.
16. Carpino, L. A.; Shroff, H.; Triolo, S. A.; Mansour, E. M. E.; Wenschuh, H.; Albericio, F. *Tetrahedron Lett.* **1993**, *34*, 7829. Two alternative easily-deblocked heteroarenesulfonamide amino acid protectants have recently been described: Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* **1996**, *118*, 9796. This work also described the greater reactivity of a sulfonamide-protected amino acid chloride relative to a urethane-protected amino acid fluoride. For a comparison of azido acid chlorides and the corresponding acid fluorides see Meldal, M.; Juliano, M. A.; Jansson, A. M. *Tetrahedron Lett.* **1997**, *38*, 2531.
17. **Pbf-MeAib-MeAib-OMe and H-MeAib-MeAib-OMe•TFA**: DIEA (102 μL, 0.6 mmol) was added to a solution of 100.2 mg (0.6 mmol) of MeAib-OMe•HCl in 900 μL of toluene. The mixture was filtered and added to 58.05 mg (0.15 mmol) of Pbf-MeAib-Cl. The reaction mixture was stirred at R.T. for 2.5 h and the resultant crude protected dipeptide ester, obtained in 63% yield, was purified by preparative HPLC to give 38 mg (52%) of the pure dipeptide ester, m.p. 170-172°C, ^{1}H-NMR ($CDCl_3$): δ 1.39 (s, 6, Me_2), 1.48 (s, 6, Me_2), 1.6 (s, 6, Me_2), 2.1 (s, 3, MeAr), 2.5 (s, 3, MeAr), 2.54 (s, 3, MeAr), 2.77 (s, 3, NMe), 2.97 (s, 2, CH_2), 3.25 (s, 3, NMe), 3.65 (s, 3, OMe); IR (KBr): 1741 (COOMe), 1642 (CON), 1306, 1132 cm^{-1} (SO_2); ES-MS: 483 (M+1), Calcd 482 (M); **Anal.** Calcd for $C_{24}H_{38}N_2O_6S$: C, 59.75; H, 7.88; N, 5.81. Found: C, 59.33; H, 7.66; N, 5.81. Cleavage of the Pbf group was carried out by treatment of 1 mg of the protected dipeptide with 100 μL of 10% dimethyl sulfide (DMS) in TFA. After 1 h deprotection was complete and the reaction mixture was worked up by ether precipitation to give 0.4 mg (86%) of the dipeptide methyl ester TFA salt, mp 162-164°C, ES-MS 231 (M+1), calcd 230 (M).

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